Antimicrobial Activity of PTK796 Tested against Gram-positive Organisms Causing Bloodstream Infections in 2009

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ABSTRACT

Background: PTK796 (PTK; 7-dimethylamino, 9-(2,2-dimethyl-propyl)-aminomethylcycline) is a novel antibacterial agent of the tetracycline family, which is under clinical development (IV and oral formulations). We evaluated the activity of PTK against Gram-positive (GP) cocci collected from bloodstream infections (BSI) in hospitals worldwide during 2009.

Methods: 3670 strains from 62 medical centers (USA, Europe and Latin America) were collected and tested for susceptibility (S) against PTK, tigecycline (TIG) and 14 other comparators by CLSI broth microdilution methods. The collection includes *S. aureus* (SA; 1,697; 37.2% MRSA), coagulase-negative staphylococci (CoNS; 640), *E. faecalis* (EF; 564; 3.0% vancomycin [VAN] resistance [R]), *E. faecium* (EFM; 368; 48.4% VAN-R), *S. pneumoniae* (SPN; 211); β-haemolytic streptococci (βHS; 170), viridans group streptococci (VGS; 9) and others (11).

Results: PTK was very active against oxacillin-S (MSSA) and MRSA with a MIC_{90} of 0.5 μg/ml for both groups (see Table). PTK activity against SA was eight- and four-fold greater than linezolid and VAN, respectively, and similar to daptomycin and TIG. CoNS exhibited slightly higher PTK MIC values ($MIC_{50/90}$, 0.25/2 μg/ml) compared to SA, with a bimodal distribution. EF (MIC_{90}, 0.5 μg/ml) and EFM (MIC_{90}, 0.25 μg/ml) were very S to PTK and R to VAN did not adversely affect PTK activity against enterococci. SPN, βHS and VGS exhibited very low PTK MIC values (MIC_{90}, 0.12 μg/ml for all groups).

	No. of isolates (cumulative %) inhibited at PTK796 MIC (μg/ml) of:						
Organism (no.)	≤0.06	0.12	0.25	0.5	1	2	4
MSSA (1,066)	5(0.5)	252(24.1)	571(77.7)	233(99.5)	5(100.0)		
MRSA (631)	2(0.3)	145(23.3)	323(74.5)	135(95.9)	12(97.8)	13(99.8)	1(100.0)
CoNS (640)	45(7.0)	161(32.2)	133(53.0)	83(65.9)	139(87.7)	75(99.4)	4(100.0)
E. faecalis (564)	32(5.7)	119(26.8)	222(66.1)	171(96.5)	18(99.7)	1(99.8)	1(100.0)
E. faecium							
VAN-S (171)	43(25.2)	67(64.3)	47(91.8)	13(99.4)	1(100.0)		
VAN-non-S (197)	60(30.5)	81(71.6)	36(89.9)	13(96.5)	4(98.5)	2(99.5)	1(100.0)
S. pneumoniae (211)	161(76.3)	42(96.2)	6(99.1)	2(100.0)			
βHS (170)	98(57.7)	60(92.9)	11(99.4)	1(100.0)			
VGS (9)	7(77.8)	2(100.0)					

Conclusions: PTK demonstrated potent activity against a large collection of recent (2009) GP isolates from BSI. Its activity was similar to that of TIG and was not affected by R to other antimicrobial classes.

INTRODUCTION

Bloodstream infection (BSI) is one of the most common nosocomial infections and the mortality rate directly attributable to this type of infection varies from 14 to 38%. In the United States (USA), nosocomial BSIs cause as many as 3.5 million additional hospital stay days per year.

The increasing rates of antimicrobial resistance are creating serious dilemmas for treatment of patients with BSI, requiring the development of new therapeutic options, advanced diagnostic tests and preventive technologies. Despite such advances, accurate empiric treatment remains critical to minimize inappropriate antimicrobial therapy that may lead to poor clinical outcomes.

PTK796 (7-dimethylamino, 9-(2,2-dimethyl-propyl)-aminomethylcycline) is a novel antibacterial agent of the tetracycline family, which is under clinical development as IV and oral formulations. We evaluated the activity of PTK796 against Gram-positive bacteria collected from BSI in hospitals around the world during 2009.

MATERIALS AND METHODS

Bacterial isolates. Isolates from patients with documented BSI were collected using a prevalence based surveillance network in 2009. A total of 3670 strains from 62 medical centers (USA, Europe and Latin America) were included in this study. The collection includes *S. aureus* (1,697; 37.2% MRSA), coagulase-negative staphylococci (CoNS; 640), *E. faecalis* (564; 3.0% vancomycin-resistant (VRE), *E. faecium* (368; 48.4% VRE), *S. pneumoniae* (211), β-haemolytic streptococci (170), viridans group streptococci (9) and other Gram-positive organisms (11).

Susceptibility testing. The organisms were tested against PTK796, tigecycline and 14 other comparators by reference broth microdilution methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M07-A8, 2009). Validated broth microdilution panels were provided by TREK Diagnostics (Cleveland, Ohio, USA). Susceptibility rates were calculated using current criteria by the CLSI (M100-S20-U, 2010) and EUCAST (2010). USA Food and Drug Administration (FDA) breakpoints were applied to establish susceptibility rates of tigecycline.

RESULTS

- PTK796 ($MIC_{50/90}$, 0.25/0.5 μg/ml) and tigecycline ($MIC_{50/90}$, 0.12/0.25 μg/ml) were very potent when tested against *S. aureus.* All strains were inhibited at ≤2 μg/ml of PTK796, except for one MRSA strain from the USA (Table 1). Overall, 37.2% *S. aureus* strains were MRSA, and MRSA and MSSA isolates had identical PTK796 $MIC_{50/90}$ values (Table 2).
- PTK796 ($MIC_{50/90}$, 0.25/0.5 μg/ml) activity against MRSA was similar to that of doxycycline ($MIC_{50/90}$, ≤0.12/1 μg/ml), but slightly lower than that of tigecycline ($MIC_{50/90}$, 0.12/0.25 μg/ml; Table 2).

RESULTS-CONTINUED

- CoNS exhibited PTK796 MIC results ($MIC_{50/90}$, 0.25/2 μg/ml) slightly higher than *S. aureus* ($MIC_{50/90}$, 0.25/0.5 μg/ml; Tables 1 and 2). All CoNS were inhibited at 2 μg/ml or less of PTK796, except for four methicillin-resistant CoNS from the USA (one strain) and Europe (three strains).
- PTK796 was slightly more active against *E. faecium* ($MIC_{50/90}$, 0.12/0.12 μg/ml) when compared to *E. faecalis* ($MIC_{50/90}$, 0.25/0.5 μg/ml) and its activity was not adversely affected by vancomycin resistance when tested against these organisms (Tables 1 and 2).
- PTK796 ($MIC_{50/90}$, 0.25/0.5 μg/ml) and tigecycline ($MIC_{50/90}$, 0.25/0.25 μg/ml; 98.9% susceptible) exhibited similar activity against *E. faecalis*, while doxycycline ($MIC_{50/90}$, 8/>8 μg/ml; 31.6% susceptible) had limited activity against these isolates (Table 2).
- All *E. faecalis* strains were susceptible to ampicillin (CLSI criteria) and linezolid, while 3.2% of strains were considered vancomycin-non-susceptible according to CLSI and EUCAST breakpoint criteria (Table 2).
- Overall, PTK796 ($MIC_{50/90}$, 0.12/0.12 μg/ml) and tigecycline ($MIC_{50/90}$, 0.12/0.25 μg/ml) had similar activity against *E. faecium,* while doxycycline (60.1% susceptible) demonstrated more limited potency against these organisms (Table 2).
- The most active compounds tested against *E. faecium* were PTK796 ($MIC_{50/90}$, 0.12/0.12 μg/ml), tigecycline ($MIC_{50/90}$, 0.12/0.25 μg/ml; 99.2% susceptible), daptomycin ($MIC_{50/90}$, 2/4 μg/ml 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/2 μg/ml; 98.1% susceptible; Table 2).
- Based on CLSI criteria, 52.7 and 48.4% of *E. faecium* were resistant to vancomycin and teicoplanin, respectively (Table 2). Vancomycin-resistant and -susceptible *E. faecium* exhibited similar PTK796 MIC distributions (Table 1).
- PTK796 ($MIC_{50/90}$, 0.06/0.12 μg/ml) inhibited all *S. pneumoniae* at ≤0.5 μg/ml (Tables 1 and 2). Overall, 9.0, 19.9, 10.4 and 13.3% of *S. pneumoniae* isolates were resistant to penicillin (≥2 μg/ml), erythromycin, clindamycin and trimethoprim/sulfamethoxazole, respectively (Table 2).
- PTK796 was very active against Group A (*S. pyogenes*; $MIC_{50/90}$, 0.06/0.12 μg/ml) and Group B (*S. agalactiae*; $MIC_{50/90}$, 0.12/0.12 μg/ml) streptococci. Group C and G streptococci were also very susceptible to PTK796, but MIC values were slightly higher (MIC_{90}, 0.25 μg/ml; Table 1).

Table 1. PTK796 MIC distribution when tested against Gram-positive isolates/groups and resistant subsets from BSI (2009).

	No. of isolates (cumulative %) inhibited at PTK796 MIC (μg/ml) of:						
Organism (no.)	≤0.06	0.12	0.25	0.5	1	2	4
S. aureus (1,697)	8 (0.4)	397 (23.8)	897 (76.5)	368 (98.2)	17 (99.2)	13 (99.9)	1 (100.0
MSSA (1,066)	5(0.5)	252(24.1)	571(77.7)	233(99.5)	5(100.0)	-	-
MRSA (631)	2(0.3)	145(23.3)	323(74.5)	135(95.9)	12(97.8)	13(99.8)	1(100.0)
CoNS (640)	45(7.0)	161(32.2)	133(53.0)	83(65.9)	139(87.7)	75(99.4)	4(100.0)
E. faecalis (564)	32(5.7)	119(26.8)	222(66.1)	171(96.5)	18(99.7)	1(99.8)	1(100.0)
E. faecium (368)	103 (28.0)	148 (90.8)	83 (90.8)	26 (97.8)	5 (99.2)	2 (99.7)	1 (100.0)
Vancomycin-susc. (171)	43(25.2)	67(64.3)	47(91.8)	13(99.4)	1(100.0)	-	-
Vancomycin-non-susc. (197)	60(30.5)	81(71.6)	36(89.9)	13(96.5)	4(98.5)	2(99.5)	1(100.0)
S. pneumoniae (211)	161(76.3)	42(96.2)	6(99.1)	2(100.0)	-	-	-
β-haemolytic streptococci (170)	98(57.7)	60(92.9)	11(99.4)	1(100.0)	-	-	-
Group A (58)	52 (89.7)	6 (100.0)	-	-	-	-	-
Group B (79)	33 (41.8)	43 (96.2)	3 (100.0)	-	-	-	-
Group C (10)	6 (60.0)	2 (80.0)	2 (100.0)	-	-	-	-
Group G (23)	7 (30.4)	9 (69.6)	6 (95.7)	1 (100.0)	-	-	-
Viridans group streptococci (9)	7(77.8)	2(100.0)	-	-	-	-	-
Corynebacterium spp. (4)	1 (25.0)	0 (25.0)	2 (75.0)	1 (100.0)	-	-	-
Listeria monocytogenes(5)	-	5 (100.0)	-	-	-	-	-

Table 2. Antimicrobial activity of PTK796 and comparator antimicrobial agents when tested against bacterial isolates from bloodstream infections.

				CLSI[a]	EUCAST[a]					CLSI[a]	EUCAST[a]
Antimicrobial agent	MIC_{50}	MIC_{90}	Range	%S / %R	%S / %R	Antimicrobial agent	MIC_{50}	MIC_{90}	Range	%S / %R	%S / %R
S. aureus (1,697)						*E. faecium* (368)					
PTK796	0.25	0.5	≤0.03 – 4	- / -	- / -	PTK796	0.12	0.12	≤0.03 – 4	- / -	- / -
Tigecycline[b]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0	Tigecycline[b]	0.12	0.25	≤0.03 – 1	99.2 / -	99.2 / 0.3
Doxycycline	≤0.12	0.25	≤0.12 – >8	98.1 / 0.2	95.5 / 2.7	Doxycycline	0.25	>8	≤0.12 – >8	60.1 / 29.1	- / -
Oxacillin	0.5	>2	≤0.25 – >2	62.8 / 37.2	62.8 / 37.2	Ampicillin	>16	>16	≤1 – >16	6.5 / 93.5	6.5 / 93.5
Levofloxacin	≤0.5	>4	≤0.5 – >4	64.7 / 34.9	64.7 / 34.9	Levofloxacin	>4	>4	1 – >4	10.3 / 87.0	- / -
Erythromycin	0.5	>2	≤0.25 – >2	51.9 / 47.1	52.5 / 47.1	Linezolid	1	2	1 – >8	98.1 / 1.6	98.4 / 1.6
Clindamycin	≤0.25	>2	≤0.25 – >2	83.2 / 16.4	82.6 / 16.8	Daptomycin	2	4	0.12 – 4	100.0 / -	- / -
Linezolid	2	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0	Vancomycin	>16	>16	0.25 – >16	46.5 / 52.7	46.5 / 53.5
Daptomycin	0.25	0.5	0.12 – 2	99.9 / -	99.9 / 0.1	Teicoplanin	16	>16	≤2 – >16	48.9 / 48.4	48.4 / 51.6
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0	*S. pneumoniae* (211)					
MSSA (1,066)						PTK796	0.06	0.12	≤0.03 – 0.5	- / -	- / -
PTK796	0.25	0.5	≤0.03 – 1	- / -	- / -	Tigecycline[b]	0.06	0.25	≤0.03 – 0.25	- / -	- / -
Tigecycline[b]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0	Tetracycline	≤2	>8	≤2 – >8	87.2 / 12.8	87.2 / 12.8
Doxycycline	≤0.12	0.25	≤0.12 – >8	98.8 / 0.2	97.1 / 1.9	Penicillin[d]	≤0.015	0.5	≤0.015 – 8	94.3 / 0.5	- / -
Levofloxacin	≤0.5	1	≤0.5 – >4	91.2 / 8.5	91.2 / 8.5	Penicillin[e]	≤0.015	0.5	≤0.015 – 8	79.6 / 9.0	79.6 / 5.7
Erythromycin	≤0.25	>2	≤0.25 – >2	75.0 / 23.8	75.7 / 23.8	Amoxicillin/clavulanate	≤1	≤1	≤1 – 16	94.8 / 4.3	- / -
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	96.2 / 3.6	95.6 / 3.8	Ceftriaxone	≤0.25	1	≤0.25 – 4	94.3 / 1.9	89.6 / 1.9
Linezolid	2	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0	Erythromycin	≤0.25	>2	≤0.25 – >2	78.2 / 19.9	78.2 / 19.9
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0	Clindamycin	≤0.25	>2	≤0.25 – >2	89.1 / 10.4	89.6 / 10.4
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0	Levofloxacin	1	1	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
MRSA (631)						Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	79.1 / 13.3	84.8 / 13.3
PTK796	0.25	0.5	0.06 – 4	- / -	- / -	Linezolid	1	1	0.25 – 2	100.0 / -	100.0 / 0.0
Tigecycline[b]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0	Vancomycin	0.25	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Doxycycline	≤0.12	0.5	≤0.12 – >8	96.8 / 0.3	92.9 / 4.0	β-haemolytic streptococci (170)					
Levofloxacin	>4	>4	≤0.5 – >4	20.0 / 79.4	20.0 / 79.4	PTK796	0.06	0.12	≤0.03 – 0.5	- / -	- / -
Erythromycin	>2	>2	≤0.25 – >2	13.0 / 86.5	13.3 / 86.5	Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
Clindamycin	≤0.25	>2	≤0.25 – >2	61.3 / 38.0	60.5 / 38.7	Tetracycline	≤2	>8	≤2 – >8	51.2 / 45.9	51.2 / 48.8
Linezolid	2	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0	Penicillin	0.03	0.06	≤0.015 – 0.12	100.0 / -	100.0 / 0.0
Daptomycin	0.5	0.5	0.12 – 2	99.8 / -	99.8 / 0.2	Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0	Vancomycin	≤0.5	1	≤0.5 – >4	98.2 / 1.8	94.1 / 1.8
CoNS (640)[c]						Erythromycin	≤0.25	>2	≤0.25 – >2	78.8 / 20.0	78.8 / 20.0
PTK796	0.25	2	≤0.03 – 4	- / -	- / -	Clindamycin	≤0.25	≤0.25	≤0.25 – >2	90.0 / 9.4	90.6 / 9.4
Tigecycline[b]	0.25	0.25	≤0.03 – 0.5	- / -	100.0 / 0.0	Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
Doxycycline	0.25	2	≤0.12 – >8	93.8 / 1.7	83.9 / 10.0	Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Levofloxacin	4	>4	≤0.5 – >4	40.8 / 56.9	40.8 / 56.9	Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Erythromycin	>2	>2	≤0.25 – >2	32.8 / 65.9	33.0 / 65.9						
Clindamycin	≤0.25	>2	≤0.25 – >2	66.1 / 33.1	63.6 / 33.9						
Linezolid	1	1	0.25 – >8	98.8 / 1.3	98.8 / 1.3						
Daptomycin	0.25	0.5	≤0.06 – 2	99.8 / -	99.8 / 0.2						
Vancomycin	1	2	≤0.12 – 4	100.0 / 0.0	99.1 / 0.9						
E. faecalis (564)											
PTK796	0.25	0.5	≤0.03 – 4	- / -	- / -						
Tigecycline[b]	0.25	0.25	≤0.03 – 1	98.9 / -	98.9 / 0.2						
Doxycycline	8	>8	≤0.12 – >8	31.6 / 14.4	- / -						
Ampicillin	≤1	2	≤1 – 8	100.0 / 0.0	99.8 / 0.0						
Levofloxacin	2	>4	≤0.5 – >4	68.6 / 30.9	- / -						
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0						
Daptomycin	1	2	≤0.06 – 4	100.0 / -	- / -						
Vancomycin	1	2	0.25 – >16	96.8 / 3.0	96.8 / 3.2						
Teicoplanin	≤2	≤2	≤2 – >16	98.0 / 2.0	98.0 / 2.0						

a. Criteria as published by the CLSI [2010] and EUCAST [2010].
b. USA-FDA breakpoints were applied [Tygacil Product Insert, 2009].
c. Includes: *Staphylococcus auricularis* (4 strains), *Staphylococcus capitis* (20 strains), *Staphylococcus caprae* (1 strain), *Staphylococcus cohnii* (3 strains), *Staphylococcus epidermidis* (315 strains), *Staphylococcus haemolyticus* (31 strains), *Staphylococcus hominis* (69 strains), *Staphylococcus lugdunensis* (15 strains), *Staphylococcus saprophyticus* (5 strains), *Staphylococcus schleiferi* (1 strain), *Staphylococcus simulans* (3 strains), *Staphylococcus succinus* (1 strain), *Staphylococcus warneri* (13 strains), *Staphylococcus xylosus* (6 strains), and unspecified coagulase-negative staphylococci (153 strains).
d. Criteria as published by the CLSI [2010] for 'Penicillin parenteral (non-meningitis)'.
e. Criteria as published by the CLSI [2010] for 'Penicillin (oral penicillin V)'.

CONCLUSIONS

- PTK796 demonstrated potent activity against a large collection of recent (2009) Gram-positive isolates from bacteremias, including MRSA and VRE.
- PTK796 activity was similar (within one doubling dilution) to that of tigecycline and was not affected by resistance to other antimicrobial classes.
- These data suggest a potentially important clinical role for PTK796 in the treatment of BSI caused by Gram-positive organisms, include multidrug-resistant strains.

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